Remarks

1. Restriction/election

I. Election

Original claims 1-106 were subject to a requirement form Restriction/election. Applicants formally elect, without traverse, the invention of Group I, claim(s) (in part) 1-3, 11, 21, 28-46, 54, 71-102, drawn to simple compositions, a method of use, and method of making composition wherein MMP inhibitors are of Group F), having core as: ***6-membered Heterocycle with 2 heteroatoms of which one atom is N0So2-C nonheterocycle*** i.e. Compound #11 of claim 29 having **thiomorpholine** molecule in the structure, classified in class 544, subclass 58.2, class 514 subclass 227.8, and Irinotecan of Topotecan together with radiation for treatment of neoplasia. Claims 4-10, 12-20, 22-27, 47-53, 55, 56, 57-70 and 103-106 have been canceled without prejudice to the filing of one or more divisional applications directed to the subject matter of the canceled claims. In addition, claims 29-42, 72-85 and 88-102 have been canceled without prejudice to the filing of one or more divisional applications directed to the subject matter of the canceled claims, in accordance with the elected invention.

II. Claim amendments

Claims 1, 44 and 87 have been amended to correspond to the elected invention. Applicants reserve the right to file one or more divisional applications directed to the subject matter canceled from the amended claims.

III. New claims

New claims 107-108 are directed to a method for treating or preventing a neoplasia disorder of the lung, using the compounds and methods of the elected invention. New claim 109 is directed to a combination for treating or preventing a neoplasia disorder of the lung, according to the compounds of the elected invention.

Therefore, claims 1-3, 11, 21, 28, 43-46, 54, 71, 86-87 and 107-109 are pending in the instant application.

2. Claims Rejected under 35 U.S.C. § 112

I. Amended claims

Claims 1-3, 11, 21, 28-46, 54 and 71-102 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the entire scope of treating or preventing neoplasia disorders encompassed by the claims. Claims 29-42, 72-85 and 88-102 have been canceled without prejudice, and are thus removed from this rejection. As to the remaining claims, claims 1, 44, and 87 have been amended. The amended claims are limited to compound 11, AG3340 in combination with Irinotecan or Topotecan for the treatment of a neoplasia disorder. For the following reasons, the rejection under 35 U.S.C. § 112, first paragraph is respectfully traversed.

A. Scope of compounds

The claims, including the amended claims, now call for compound 11, AG3340, a specific MMP inhibitor in combination with Irinotecan or Topotecan, which are well known antineoplastic agents. Therefore, the claims are sufficiently clear and concise.

B. Scope of the conditions

The claims, including the amended claims, now call for a method of treating or preventing a neoplasia disorder, using a specific MMP inhibitor in combination with Irinotecan or Topotecan, which are well known antineoplastic agents. Therefore, the claims, including the amended claims, now are directed to well defined neoplastic disorders, and not all disorders relating to degradation of the extracellular matrix.

C. Enablement of Claims

The specification asserts that the recited combinations of compounds are effective. Page 11, lines 15-24 recites:

The methods and combinations of the present invention provide one or more benefits. Combinations of MMP inhibitors with the compounds, combinations, agents and

therapies of the present invention are useful in treating and preventing neoplasia disorders. Preferably, the MMP inhibitor or inhibitors and the compounds, combinations, agents and therapies of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations.

Thus, the claims are enabling for their asserted utility. See MPEP 2164.01(c); and TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS,

2. Reasons For Lack Of Enablement: Undue Experimentation Needed To Make And Use The Invention:

...

ii. How to Use
If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. Section 112, is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); and *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643
(CCPA 1965); see also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112. The applicant need not demonstrate that the invention is completely safe. See also 35 U.S.C. Section 103 , Utility Guidelines.

The articles asserted in Paper Number 14 relate point to enablement. Heath et al (PubMed Abstract 10852638, and Drugs 2000 May, 59/5, 1043-55) states that "based on promising preclinical studies, synthetic MMPI have been developed and taken into clinical trials. These include marimastat, BAY-129566, CGS-27023A, **prinimostat (AG-3340),** BMS-275291 and metastat (COL-3)." (emphasis added).

Belotti et al.(PubMed Abstract: 10669951; Int. J. Biol Markers 1999 Oct-Dec; 14/4, 232-8) states: "Treatment with MMP inhibitors alone or in combination with cytotoxic therapy is an interesting novel approach to control tumor progression."

Similarly, the quotation from Liekens et al. (PubMed Abstract: 11172729, and Biochem Pharmacol 2001 Feb 1, 61/3, 253-70) admits that synthetic inhibitors of cell invasion, specifically AG3340, may offer a potential therapy for cancer and angiogenic diseases.

Hidalgo et al. (PubMed Abstracts: 11158186, and J Natl Cancer Inst 2001 Feb 7, 93/3, 178-93) is relevant to the design of clinical trials, but not to the issue of enablement. See MPEP 2107.03:

> HUMAN CLINICAL DATA
> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans). Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

Therefore, it is respectfully requested that the rejection under 35 U.S.C. § 112, first paragraph, as applied to the claims presented be withdrawn.

II. New claims

The official letter dated July 17, 2002 (Paper Number 14) states at page 3, second paragraph, that the specification is enabling as a method of treating neoplasm related to lung. New claims 107-108 are directed to a method for treating or preventing a neoplasia disorder of the lung, using the compounds and methods of the elected invention. New claim 109 is directed to a combination for treating or preventing a neoplasia disorder of the lung, according to the compounds of the elected invention.

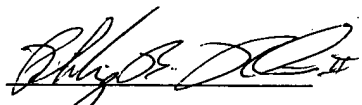
Without acquiescing to the propriety of the instant rejection, it is asserted that new claims 107-109 are enabled, and it is respectfully requested that claims 107-109 be allowed.

3. Conclusion

For the foregoing reasons, it is respectfully submitted that claims 1-3, 11, 21, 28, 43-46, 54, 71, 86-87 and 107-109 are in condition for allowance, and it is requested that the application be passed to issue.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, he is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,



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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT :. McKearn et al.

GROUP ART UNIT: 1624

SERIAL NO.: 09/857,995

EXAMINER: Sudhaker B. Patel

FILED: October 5, 2001

DOCKET NO.: 3167/5

FOR: Method of Using MMP Inhibitors and One or More Antineoplastic Agents as a Combination Therapy in the Treatment of Neoplasia

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents and Trademarks, Washington D.C., 20231.
Philip B. Polster II
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Date: October 17 2002

Version Marked to Show Changes Made

1. (amended) A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of **[a]** **the** matrix metalloproteinase inhibitor **N-hydroxy-2,2 dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl] 3-thiomorpholinecarboxamide** and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of **[anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine, goserelin,]** irinotecan**[, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa,]** **and** topotecan**[, toremifene, vinorelbine,**

selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO)].

44. (amended) A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of radiation therapy, **[a]** the matrix metalloproteinase inhibitor **N-hydroxy-2,2 dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl] 3-thiomorpholinecarboxamide**, and one or more antineoplastic agent, wherein said antineoplastic agents are selected from the group consisting of **[anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine, goserelin,]** irinotecan**[, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa,]** and topotecan**[, toremifene, vinorelbine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO)].**

87. (amended) A combination comprising **[a]** the matrix metalloproteinase inhibitor **N-hydroxy-2,2 dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl] 3-thiomorpholinecarboxamide** and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of **[anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine, goserelin,]** irinotecan**[, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa,]** and topotecan**[, toremifene,**

vinorelbine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO)].